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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: [Docket No. 99D-0529] Draft Guidance for Industry on Changes to an Approved NDA or ANDA

Dear Madam or Sir:

PDA is pleased to have the opportunity to provide comments on the draft Guidance for Industry entitled Changes *to an Approved NDA or ANDA*, June 1999, the availability of which *was* announced in the *Federal Register* on June 28, 1999. We trust PDA's comments will assist FDA in issuing a refined guidance which will reflect current thinking of both the agency and industry on how to report changes to an approved NDA or ANDA under the proposed revision to the drug regulations pertaining to supplements and other changes to an approved application published elsewhere in the same issue of the *Federal Register*. [Note: PDA wili submit separate comments on this proposed rule.]

PDA strives to assess regulatory issues primarily on their scientific and technical merits. To facilitate FDA review, our comments are divided into two parts: this cover letter which describes our general concerns, and a table which explains specific comments by section and line number.

" Validate " Term

We recognize that FDA is using the word "validate" (assess the effect of a manufacturing change) in the same sense as Congress's use of this word in FDAMA. We understand that within the guidance, it is not intended to have the same meaning as the CGMP definition of "validate." However, use of the same word for different meanings could result in unnecessary confusion and could create the potential for regulatory "drift." PDA recommends replacing "validate" with "assess" in the guidance document.

Regulatory Relief

PDA appreciates that FDA has attempted to provide some regulatory relief in the guidance (e.g., lines 191-194 and 447-456). Overall, PDA is concerned that the guidance which provides the potential of increased flexibility does not provide for substantial regulatory relief. As currently

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written, the guidance provides minimal reduction in reporting requirements and in some cases, an increase (e.g., lines 584, 711-713 and 794-799). In particular we are concerned about the number of changes classified as preapproval supplements. This burdensome categorization is often not warranted and we recommend more frequent use of the CBE-30 supplement.

Sterility Assurance Reporting Requirements

We recognize that changes that significantly affect sterilization are considered major changes requiring prior approval supplements. However, we encourage FDA to re-evaluate the examples used in the guidance document and reconsider if many of these can be lower reporting categories. In addition, many of the examples provided for sterile process changes should not require regulatory reporting but should be documented internally by the applicant and available for field CGMP inspections.

SUPAC Flexibility

The SUPAC documents have provided some regulatory relief for sponsors by reducing the reporting requirements and as such these principles should be incorporated into the guidance. We note that the guidance does refer to SUPAC (e.g., lines 32-34). To assure that the efforts gained by SUPAC are not lost, we recommend that the timeframe between the final guidance and the revision of SUPACs be kept short to minimize confusion during this period. During this transition, the industry would use whichever document provides the least burdensome regulatory requirement (i.e., the lowest reporting category).

Comparability Protocol

The concept of comparability provides for reduced regulatory burden and PDA recommends that the guidance clearly state that comparability protocols can be submitted in either the original market application or as a supplement, post approval; this is consistent with the intent and actual practice. We understand that FDA intends to issue separate guidance on comparability protocols. We strongly encourage FDA to allow comparability protocols to be used in the broadest way possible so they may offer the reduction in regulatory burden they were designed to provide. In addition, it would be helpful if FDA would define the principles for establishing comparability.

Specific Terminology

Wherever possible, FDA should use specific terms and avoid the use of vague or broad terms or phrases such as “any change” or “may.” These “catch-all” phrases can be easily misinterpreted by field inspectors. In fact, the industry is experiencing this today. In our comments, we have suggested adding the modifier “significant” or “significantly” in several instances to sharpen the intended meaning. Since the term “significant” is itself undefined, PDA suggests that in the context we use it in our comments “significant” means “likely to adversely affect the identity,

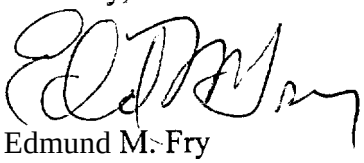
strength, quality, purity or potency of the related product."

Filings versus Inspections

PDA believes that FDA should rely more heavily on on-site review of data conducted by FDA investigators during inspections. Much of the data requested by the guidance document can be reviewed during the field inspection process, reducing the regulatory burden for the sponsor (e.g., lines 398-399 and 501-504).

We appreciate the opportunity to contribute to the development of this important guidance for industry. Please contact me if you have any questions.

Sincerely,



Edmund M. Fry
PDA President

Attachment

Section	Line	Comment	Rationale
I. Introduction	*32-34*	We urge FDA to expedite this exercise as we anticipate much confusion and additional regulatory burden in the transition.	It is stated that the proposed rule and draft guidance documents will supersede prior published guidance such as SUPACs. We understand that CDER intends to update the prior published guidances to make them consistent with this guidance.
II. Reporting Categories	*54-56*	We recognize that this situation should not be abused, but we feel that this requirement is overly stringent. Instead, we recommend applicants contact their FDA reviewing division to determine if an expedited review based on extraordinary hardship is appropriate.	Expedited review based on an extraordinary hardship should not be limited to changes made necessary by catastrophic events or events that could not be planned.
Same	*82-84*	We recommend a revision from "A comparability protocol must be submitted., ." to "*If not approved as part of the original application, a comparability protocol must be submitted...*"	There could be circumstances where a comparability protocol(s) is submitted and approved as part of an original application. We understand that FDA intends to issue separate guidance on comparability protocols. We strongly encourage FDA to allow comparability protocols to be used in the broadest way possible so they may offer the reduction in regulatory burden they were designed to provide.
III. General Requirements	97-100	Move this information to "X. Labeling,"	These comments are specific to labeling issues and are not appropriate for the general requirements section.

Section	Line	Comment	Rationale
IV. Assessing the Effects of Manufacturing Changes	104-114	While we recognize that section 506A(c)(1) of the act contains these terms, we recommend replacing the terms "validate" or "validation" with "*assess*" or "*assessment*" throughout the draft guidance document.	The term *validate* or *validation* used in this section means assessing the change, and is not intended to mean the same as the CGMP definition of validation (footnote #5). We feel the inconsistent use of the same terms for different meanings lends itself to unnecessary confusion.
Same	110-111	We recommend a revision from "...determined to be appropriate by FDA..." to "*...as specified in this or other FDA guidances...*"	Added clarity
IV. Assessing the Effect of Manufacturing Changes 1. Conformance to Specifications	115-128	The issue of container-closure integrity testing needs clarification.	Is there a need to integrity test the identical container-closure when used on more than one product? Once a specific container-closure is tested, this information should be allowed to be used in other applications.
Same	123	Change "...including container closure systems..." to "*including the packaging components of container closure systems...*"	The specifications referenced in this section are meant to apply to the individual packaging components that comprise the container closure system, and not the assembled system itself.
IV. Assessing the Effect of Manufacturing Changes B. Equivalence	154	Change heading from "B. Equivalence" to *"3. Comparability"*	Consistency (e.g., comparability protocol)
Same	154-166	We found this section to be confusing; we propose deletion of lines 158-166.	We believe the onus is on the industry to determine equivalency/comparability.

Section	Line	Comment	Rationale
Same	155-157	Change "of the drug product" to *"of the material produced at the processing step where the change is made or at a subsequent step."*	Equivalence is demonstrated at the processing step where the change is made or a subsequent step. According to BACPAC I, equivalence may be demonstrated at a drug substance intermediate, and does not require assessment of the drug product.
Same	158	We recommend changing "...equivalent.. ." to "*...comparable...*"	Consistency
IV. Assessing the Effect of Manufacturing Changes C. Adverse Effect	167	Change the heading from "C. Adverse Effect" to "4. *Adverse Effect"*	Format consistency
V. Components and Composition	191-194	We are pleased that FDA recognizes that the SUPAC documents provide regulatory relief. In addition, we feel that FDA should extend this to include the PAC-SAS guidance as well.	
VI. Sites	195	We recommend consistency in or clarification of the various terminology used.	This section refers to sites, facilities, establishments and campuses. The various terminology can become confusing.
VI. Sites A. General Considerations	200	Insert "primary" in front of "packaging" to read *'primary packaging materials."*	Listing control laboratories for secondary packaging components represents an increased regulatory burden.
Same	211-221	Delete lines 2 1 l-22 1	Duplication of information already provided in lines 248-26 1.

Section	Line	Comment	Rationale
Same	213-215	Item (2) should be deleted.	The driver here should be a satisfactory CGMP inspection for the type of operation in question. With current verbiage (manufacture was discontinued at some time) confusion will result from real-life situations (e.g., campaigned products). Whether or not a type of operation has been stopped and is now being restarted should not be the deciding point; instead, whether or not the facility has a satisfactory CGMP inspection for the type of operation in question is the key.
Same	250-252	Delete lines 250-252 beginning "for the type of operation being moved used to be performed.. ."	The driver here should be a satisfactory CGMP inspection for the type of operation in question. With current verbiage (manufacture was discontinued at some time) confusion will result from real-life situations (e.g., campaigned products). Whether or not a type of operation has been stopped and is now being restarted should not be the deciding point; instead, whether or not the facility has a satisfactory CGMP inspection for the type of operation in question is the key.
Same	259	Delete example (2).	This represents a GMP issue that is regulated by the field.
Same	266-269	Provide examples of modified-release parenteral site changes that would fall into this category.	It is not clear if modified release parenteral products (e.g., depot formulations) are included in this category.

Section	Line	Comment	Rationale
Same	271-276	Delete item 5.	A move to a site that has been inspected by FDA for the type of operation that is being moved should be a moderate change (Supplement-Changes Being Effected). This includes transfer of an aseptically processed sterile drug substance or sterile drug product.
VI. Sites C. Moderate Changes 1. CBE-30 Days	284	Add example: *"A move of drugproduct labeling to a site on the same or different campus, when the new facility has never been inspected by the FDA for drug product labeling.*"	The CGMP compliance practices present in the existing facility would be easily transferred to the new facility, and the drug product labeling operation represents minimal product risk. The 30-day effectivity provides FDA the time to complete a compliance inspection of the new facility, if necessary, without unnecessary delay of implementation by the applicant.
Same	288-291	Changes within a single facility or same campus for the manufacture of sterile drug substances or drug product should be reported within an annual report.	Since the requirement for a satisfactory CGMP inspection will have already been met, requiring a CBE-30 for movement of product within the same building or campus represents an increased regulatory burden over current practice.
Same	294-300	We recommend this item be considered a minor change (Annual Report).	This category is unnecessarily restrictive and is more than what is the current practice today. It is unlikely that such a change will have an adverse effect.

Section	Line	Comment	Rationale
VI. Sites C. Moderate Changes 1. CBE	*303-309*	We recommend items a and b be considered as minor changes (Annual Report).	This requirement represents an unnecessary regulatory burden and is inconsistent with current guidance if the new site has been operating in compliance with CGMPs and there are no changes in the chemistry, control strategy, analytical methods or reagents. We recommend that this be changed to an annual report notification and permit detailed information supporting the changes to be maintained by the manufacturer and available for FDA inspection.
VI. Sites D. Minor Changes	*333*	Move item 7 to under item 4. Change text to *"Change in the floor plan which results from a facility 'build out'."*	Format change would flow better after the example for the same campus changes. Change in verbiage eliminates unnecessary reporting of insignificant changes to floor plans which are covered under CGMPs and concentrates on facility build out.
Same	*335-336*	We recommend deletion of lines 335-336.	Item is vague and provides no additional value.
VII. Manufacturing Process A. General Considerations	*347-35 1*	Delete these lines. The inference is that the applicant is not able to adequately evaluate the potential adverse effects of a change.	The burden of risk falls on the applicant to appropriately evaluate the effects of the change. The applicant has the most first-hand knowledge of the issues for a product/process, and per the original validation work included in the initial (A)NDA, should be granted the scientific and technical ability to evaluate the change.

Section	Line	Comment	Rationale
Same	357	We recommend alternate wording such as "*changes that significantly impact sterility assurance.*"	This section states that "Changes *may affect* product sterility assurance" is vague, broad, and restrictive and could be interpreted extremely conservatively.
VII. Manufacturing Process B. Major Changes C. Moderate Changes D. Minor Changes	361-491 517-520	Clarify if this section is meant to apply to API and/or drug product. Examples: Lines 408-414 include what appear to be both API and drug product examples, but lines 415-420 are specific to API. Lines 468-473 are not clear as to whether API or drug product is covered.	Confusion will result in interpretation
VII. Manufacturing Changes B. Major Changes	370	Change "that may affect" to "*that significantly impact.*"	The "Changes that *may affect* product sterility assurance" is vague, broad, and restrictive and could be interpreted extremely conservatively.
Same	373	We recommend the revision of "Changes in the sterilization method(s)." to • *Change of sterilization method(s) for components (e.g. change from steam to dry heat).* • *Change of the sterilization method(s) (e.g. change from terminal to aseptic processing).*	
Same	374	We recommend adding the word "significant" to read: "*Addition, deletion, or substitution of significant steps in an aseptic processing operation.*"	Clarification

Section	Line	Comment	Rationale
Same	376	We recommend clarifying this by adding a separate statement addressing components under section C.	For sterilization of components, this type of change should be considered a moderate change (Changes Being Effected).
Same	380-383	Add *"significant"* prior to the words "different materials" in line 38 1. Delete "or deletion of equipment from an aseptic processing line." We recommend that this change be a CBE.	This change is overly burdensome and is more than what is the current practice today.
Same	384-385	We recommend revision to add "or isolator": *"Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling."* In addition, we recommend this change be considered a moderate change (Changes Being Effected).	
Same	386-388	We recommend revision from "lengthens the overall process time" to *"lengthens the overall process time by more than 50% of cycle time."*	
Same	392	We recommend deleting the phrase "into additional aseptic filling shifts."	
Same	398-399	We recommend deletion of this sentence.	This requirement increases the regulatory burden on industry and would result in a significant number of additional prior-approval supplements. This change is currently covered by review of data in CGMP inspections.
Same	400-40 1	For clarification, we recommend revision from "filter size" to *'Jilter pore size."*	

Section	Line	Comment	Rationale
VII. Manufacturing Process B. Major Changes	407	Revise wording to: *"Establishment of a new master cell bank or seed only if it requires additional transformation."*	
Same	408-420	For clarity, separate out examples for drug substance and drug products under its respective categories.	Ease of review
Same	414	Delete this requirement since this is addressed in line 418.	Duplication
Same	416	Revise wording from "Any process.. ." to *"Any significant process.. ."*	Otherwise it could be interpreted to include all small and insignificant changes.
Same	418-419 43 1-432	Verbiage in lines 4 18-419 is too general and is confusing when compared to lines 43 l-432. Clarification is necessary.	A change in process is a change in a solvent reagents, process parameters or purification procedures (Ref. BACPAC I). Bulk drug substance process changes are most likely to result in changed impurity profiles; the guiding principle is that the change must be assessed and material before and after the change must be equivalent. Examples: change in solvent or reagents (prior approval); change a process parameter (e.g. temperature, pH, stoichiometric time))tighten annual report) (widen-CBE).
VII. Manufacturing Changes C. Moderate Changes	431	Revise wording from "Any change.. ." to *"Any significant change.. ."*	"Any process" could be interpreted to include all small and insignificant changes, which increases regulatory burden.
Same	439	Revise "or size" to *"or pore size"*	

Section	Line	Comment	Rationale
Same	458-459	Delete the phrase ". . .do not require additional aseptic filling shifts or.. ."	
VIII. Specifications A. General Considerations	496	Ensure "specification" definition is consistent with ICH."	Add "the list of' to "(i.e., the list of tests, analytical procedures. . .)."
Same	501-504	Delete the last sentence in this section.	Specifications associated with monitoring of the production environment are available for review on-site in a CGMP inspection.
VIII. Specifications B. Major Changes	517	Delete "except as otherwise listed." and replace with *"for starting materials introduced after the final drug substance intermediate, the final intermediate, the API, non-compendial components, and the drug product."*	Relaxing of acceptance criterion is most critical for significant parts of the final molecule introduced after the final intermediate, the API, non-compendia1 components, and the drug product. Lines 540-543 cover all other materials used in API manufacturing, and line 567 (as suggested to be altered below) will cover any drug product compendia1 components.
VIII. Specifications C. Moderate Changes	538	Change to *"Any changes in a regulatory analytical procedure for which the change impacts the method validation package."*	Minor revisions are often made in regulatory analytical procedures (e.g., typographical corrections, clarifications).
Same	551-562	Item 2a should be a minor change (Annual Report).	It provides either the same or increased assurance of identity, strength, quality, purity, or potency of the material/drug.
VIII. Specifications D. Minor Changes	567-571.	Change 567 to *"Any change made to comply with an official compendium."* Delete balance of sentence from "that is consistent.. .in the approved application."	Our recommendation is consistent with current requirements. The additional wording would increase the regulatory burden. Use the compendia1 review and comment process to influence these changes.
Same	585	Delete item 5.	This provides increased regulatory burden and this requirement is not the current industry practice.

Section	Line	Comment	Rationale
IX. Package A. General Considerations	591-595	Delete these lines. The inference is that the applicant is not able to adequately evaluate the potential adverse effects of a change.	The burden of risk falls on the applicant to appropriately evaluate the effects of the change. The applicant has the most first-hand knowledge of the issues for a product/process, and per the original validation work included in the initial (A)NDA, should be granted the scientific and technical ability to evaluate the change.
Same	597-599	Clarify example "(1)," specifically the phrase "with that particular dosage form." Does "particular dosage form" imply product family (e.g., cephalexin) or dosage type (e.g., solutions, suspensions) or both?	Wording is unclear.
Same	597-599; 616	Add *"Once this change has been approved subsequent changes ofproductfamily strengths to packaging components made of the same composition may be filed as a supplement – changes being effected."*	Once a particular strength of a product family (e.g., 125 mg/mL cephalexin for suspension) has been approved for a new packaging component composition, all other strengths of the same product (e.g., 300 mg/mL, 500 mg/mL) should be easily reported.
IX. Package B. Major Changes	611-616	We recommend revision from "... has never been approved by CDER for use with that particular liquid dosage form or semisolid dosage form" to *"has never been approved by CDER for use with similar drug products."*	Under item 1, "that particular liquid form" needs clarification. As currently written, it assumes that this refers to similar family of liquid dosage forms.
Same	626	Change ". ..that may affect.. ." to "*. . .that significantly impact. . .*"	The statement ". . .that may affect.. ." is vague, broad and restrictive and could be interpreted conservatively, resulting in increased regulatory burden.
Same	638-639	Change sentence to read *"Significant change in size and/or shape of a container for a sterile drug substance or sterile drug products which impacts sterility assurance (e.g. change in finish size)"*	Original wording is too broad.

Section	Line	Comment	Rationale
IX. Package C. Moderate Changes	647-648	Change sentence to read *"A change in primary or secondary components that is intended to provide additional protection to the drug product, except as otherwise listed."*	Additional clarification.
Same	649	Add *"1 b. Significant change in size and/or shape of container for a sterile drug substance or drug product which doesn't impact sterility assurance."*	
Same	After line 652	Add *"2b. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has been approved by CDER for use with similar drug products."*	
IX. Package D. Minor Changes	657-660	It would be helpful for FDA to clarify if there is a difference between packaging equivalency protocol versus comparability protocol.	
Same	661	Delete ". . .containing the same number of dose units"	For nonsterile dosage forms, the count of the bottle should be allowed to be changed along with the size/shape. The current verbiage should allow the size of the bottle to increase (and therefore more headspace) but the count to not equivalently change; this would appear to present a more significant potential for adverse effect than for both to change in unison.

Section	Line	Comment	Rationale
Same	672-673	Change to *"Changes in packaging materials used to control odor (e.g., charcoal packets) or moisture (e.g., desiccants). This includes changes to both the agent (e.g., charcoal, silica) and the packet (e.g., canister)."*	The clarification details the extent of the example and adds desiccants as an equivalent packaging change. The introduction verbiage still requires the desiccant to provide the same or better protective properties.
Same	679	Add "colorant" to *"'A change in an antioxidant, colorant, stabilizer.. ."*	Colorants are similar in nature to antioxidants and stabilizers in resin formulations.
Same	710	Add • *"A change in or addition of a seal (e.g. heat induction seal)."*	Additional example.
Same	71 l-713	Delete item 7.	This is an additional requirement that is overburdensome and is not the current industry practice.
Same	After 713	Add another item *"changes in component vendors without any other signijcant change in the component."*	Additional example.
IX. Package D. Minor Changes	765	After sentence, add *". . .or to comply with an official compendium."*	This is the current industry practice e.g., to comply with USP revisions.
XI. Miscellaneous Changes A. Major Changes	776-777	Delete item 2.	This is covered under line 370.
Same	778	At the end of the sentence, add *". . . , if not approved in the original application."*	The additional wording further clarifies actual practice.
Same	779-78 1	Item 4, delete ". . .or based on pilot batch data."	This is not a current CFR 3 14 requirement.

Section	Line	Comment	Rationale
XI. Miscellaneous Changes C. Minor Changes	791	Delete "on full production batches."	Current regulations allow extension of the expiration date based on full shelf-life data obtained from a protocol approved in the application. There is no requirement for the data to be on full production batches. This requirement is more stringent than under 3 14.70 today and is unwarranted.
Same	793	Add *"or tests"* after the word "time points" to the phrase "Addition of time points." Clarify that an approved protocol is not rendered unapproved by adding tests and/or time points in an annual report.	Adding a test to a stability protocol should be permitted in an annual report as this provides additional assurance that the product is being evaluated over its shelf life. The clarification point around an approved protocol is important to ensure that appropriate interpretation of these changes to the approved protocol.
Same	794-799	Delete item 3 on Reference standards.	This is a more stringent requirement and is not the current industry practice. Such a need would increase the regulatory burden.
Glossary of Terms	806	Add definitions for "Comparability Protocol," "Campus," "Site," "Facility," "Establishment," and "Pharmaceutical Equivalence," as appropriate.	If these terms remain in the guidance they need to be well defined in the glossary.
Same	*825-829*	Add *"or breakage"* after "covalent bond formation"	Breaking covalent bonds is a significant chemical change that should differentiate the final intermediate from the drug substance. This comment was also made to BACPAC 1.
Same	*865*	Definition of "specification" should be consistent with ICH.	

Section	Line	Comment	Rationale
Same	865	Add "the list of' to "*The quality standard (i.e., the list of tests, analytical procedures and acceptance criteria) . . .* "	This clarification is consistent with the ICH definition and helps to clarify that the sum of all of the individual tests/procedures/acceptance criteria constitutes the specification.
Same	869-87 1	We recommend replacing the term" validate" with "*assess.*"	The term "validate" which is not intended to mean the same as the CGMP definition of validation. We feel the inconsistent use of the term for different meanings lends itself to unnecessary.